Claims 52 and 62 were objected to under the Sequence Rules. These claims have been cancelled. The objections have therefore been rendered moot.

Claim 90 was objected to for a typographical error. Claim 90 has been cancelled. The objection has therefore been rendered moot.

Claims 32, 33, 36-47, 51-55, 57-66, 68, 69, 82, 85, 89 and 92 stand rejected under 35 U.S.C. § 112, first paragraph, based upon an assertion that they contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. All of these claims except for claims 38-43 and claim 82, have been cancelled. The rejection has thus been rendered moot as to the cancelled claims. As to claims 38-43 and 82, this rejection is respectfully traversed for the following reasons.

Claim 38 is the sole independent claim among claims 38-43. Claim 38 requires the "presence of an immobilized amount of polypeptide containing a first amino acid sequence which provides the binding activity of Heparin-II binding domain of fibronectin and a second amino acid sequence which provides the cell-binding activity of the CS-1 domain of fibronectin, said immobilized amount of polypeptide being effective to increase the frequency of transduction of the hematopoietic cells by the retrovirus vector." The specification as originally filed reasonably conveys to the ordinarily skilled artisan that the inventors had possession of this invention. First, it is noted that claim 38 does not include the phrase "sufficiently similar to SEQ. ID. NO. 1 or SEQ. ID. NO. 2" as a basis for defining a genus of amino acid sequences. Rather, the polypeptide has the binding activity of the Heparin-II domain of fibronectin, and the cell-binding activity of the CS-1 domain of fibronectin. The thus-defined fibronectin polypeptides and close analogs are fully described in the present application. For example, at page 5, the application teaches:

> The fibronectin and/or fibronectin fragments can be derived from naturally-occurring materials or can be synthetically derived (e.g. genetically engineered by recombinant or chemical synthesis techniques), or derived from a combination of naturally-occurring

and synthetic materials. In addition, it will be understood that the fibronectin polypeptide or polypeptides utilized in the invention may include mutations to the naturally-occurring fibronectin amino acid sequence which nonetheless provide functional polypeptides having the adhesion properties necessary for achieving enhanced transduction in accordance with the invention.

As well, at page 6, the application teaches:

> In accordance with more specific aspects of the above-mentioned embodiments of the invention, the fibronectin or fibronectin fragment utilized will contain a first amino acid sequence which provides the retroviral-binding activity of the Heparin-II-binding domain of fibronectin, and a second amino acid sequence which provides the cell-binding activity of the CS-1 domain of fibronectin. The use of these two binding domains of fibronectin together has proven to very significantly enhance the transduction efficiency of the target cells by the retrovirus.

Further, at page 15, the application teaches:

> In this regard, the capacity of a virus to bind to the amino acid sequence of the Heparin-II binding domain and thus to serve effectively in the invention can be readily ascertained using routine procedures such as those described in Examples 8 and 9 below. Generally speaking, these assays determine the extent to which virus particles are bound to immobilized polypeptides containing the Heparin-II binding domain, so as to resist washing from the immobilized polypeptide matrix. Briefly, for instance, a virus-containing supernatant can be incubated in a well containing immobilized polypeptide including the fibronectin Heparin-II binding domain. The well is then extensively washed with physiologic

saline buffer, after which target cells to the virus are incubated in the well to determine the level of infectious activity remaining in the well. The reduction in infectious activity, or titer, relative to the initial viral supernatant is assessed and compared to that of a similar control run (e.g. using a BSA-coated well). A significantly higher titer remaining in the Heparin-II domain containing well as compared to the control well signifies that the subject virus is suitable for use in aspects of the invention. To facilitate this screening procedure, the viral vector may contain a selectable marker gene, as discussed above.

Still further, in the passages spanning pages 16 and 17, the application teaches:

> Fibronectin fragments which contain both the CS-1 cell adhesion domain and the Heparin-II binding domain, for example as included in about a 30 or 35 kd fragment (30/35 FN) and in various recombinant fragments as reported in the Examples below, have been found to significantly enhance the efficiency of gene transfer into hematopoietic cells in work thus far, and are preferred for use in the invention. It will thus be understood that, broadly speaking, the fibronectin-related polypeptide or polypeptides utilized in the invention will provide an amino acid sequence providing the cell-binding activity of the CS-1 cell adhesion domain of fibronectin as well as an amino acid sequence of the Heparin-II binding domain of fibronectin which binds the virus. The skilled artisan will recognize that the necessary cell- and virus-binding activities can be provided both by native amino acid sequences of these functional fibronectin domains and by amino acid sequences which differ from the native sequences yet are sufficiently similar to exhibit the cell-binding and viral-binding activities. These similar amino acid sequences will exhibit substantial sequence homology to their corresponding

native sequences, and can include those in which amino acids have been deleted, substituted for and/or modified while nonetheless providing an amino acid sequence with the desired cell-binding or viral-binding characteristic.

As to cell-binding activity, the application similarly teaches, in the paragraph spanning pages 17 and 18, that:

> Cell-binding to modified or mutant forms of the CS-1 cell adhesion domain of fibronectin, or to other cell-binding polypeptides, can likewise be assayed using conventional procedures. For example, such procedures include those described in *Nature* 352: 438-441 (1991). Briefly, the cell-binding polypeptide is coated on plastic dishes and the cell population to be assayed is overlayed in medium for 30 minutes to 2 hours. After this incubation period, cells non-adherent to the protein are retrieved, counted and assayed for viability. Cells adherent to the polypeptide are also retrieved using trypsin or cell dissociation buffer (e.g. Gibco), counted and viability tested. In some cases, for example for hematopoietic colony forming cells, the cells are further cultured for an additional 12-14 days to ascertain the colony forming characteristics of the cells. The percentage of adherent cells is then calculated and compared to standard to a standard control such as bovine serum albumin (BSA) coated plastic dishes. Substantial binding of the target cells to the assayed polypeptide provides an indication that the polypeptide/cell combination is suitable for the invention, and the polypeptide can be coupled to the retroviral binding fragment from fibronectin to produce a construct of the invention for enhancing the infection of the target cells by the viral vector.

In view of these and other teachings in the application regarding the use of fibronectin and fibronectin analogs having the binding capacities claimed, it is submitted that the written description requirement is fully satisfied as to independent claim 38 and its dependent claims 39-43.

In respect of claim 82, it is believed that the original language is also fully supported by the specification. However, in order to moot the rejection and advance this prosecution, the passage of claim 82 found to be objectionable by the Examiner has been deleted.

In view of the foregoing amendments and remarks, reconsideration and withdrawal of the rejections under 35. U.S.C. § 112, first paragraph, based upon the written description requirement, are solicited.

Claims 32, 33, 36-47, 51-55, 57-66, 68, 69, 82, 85, 89 and 92 stand rejected under 35 U.S.C. § 112, first paragraph, based upon assertion that the specification is not enabling for these claims. All of these claims, except for claims 38-43 and 82, have been cancelled. This rejection has therefore been rendered moot as to the cancelled claims. As to claims 38-43 and 82, this rejection is respectfully traversed for the following reasons.

With regard to claims 38-43, as noted above, the present application contains ample teaching with respect to fibronectin fragments and close analogs thereof exhibiting the binding activities claimed. These teachings involve well-known facts and procedures in the biotechnology arts. Accordingly, the skilled artisan would have absolutely no difficulty in finding a range of polypeptide fragments utilizable in the invention of claims 38-43. In addition, with regard to claim 82, while it is believed that the original language is fully enabled, the passage in claim 82 containing the "sufficiently similar" limitation has been cancelled to expedite the present prosecution. For these reasons, it is believed that the above-noted enablement rejection under 35 U.S.C. § 112 has been comprehensively addressed. Its withdrawal is solicited.

Claims 24, 25, 32-37, 42, 44-56, 62-66 and 84-86 stand rejected under 35 U.S.C. § 112, first paragraph, based upon an assertion that the specification is enabling only for those illustrative claims set forth on page 8 of the Office Action. All of

these claims, except for claim 42, have been cancelled. Therefore, this rejection has been rendered moot with respect to all cancelled claims. As to claim 42, this rejection is respectfully traversed for the following reasons.

Claim 42 is ultimately dependent upon claim 38, and relates to cellular populations. Cellular populations such as those claimed are fully enabled and have a number of uses including therapeutic, research and other uses. These uses are taught in the application and/or would be clear to those skilled in the art. Accordingly, withdrawal of this rejection as applied to claim 42 is solicited.

Claims 23, 33, 37, 41, 49, 52, 55, 57, 60, 62, 65, 82, 85, 89 and 92 stand rejected under 35 U.S.C. § 112, second paragraph, based upon an allegation that they are indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention. All of these claims, except for claims 41 and 82, have been cancelled. Therefore, this rejection has been rendered moot as to the cancelled claims. As to claims 41 and 82, this rejection is respectfully traversed for the following reasons.

This rejection was applied to claim 41 based upon an assertion that "low density" in the context of claim 41 would be indefinite to the skilled artisan. However, the expression "low density, mononuclear cells" in the context of hematopoietic cells as claimed would be clear to the skilled artisan. This term has long been and continues to be common usage understood by those skilled in the art. For example, see U.S. Patent Nos. 5,004,681 (see e.g. Fig 3B; Col. 13, line 55+; Col. 38, line 62+); 5,807,686 (see e.g. claims 1, 4, 6 and 8); 5,409,825 (see e.g. Col. 4, line 62+); 5,672,346 (see e.g. Col. 7,. line 7+). The following literature articles show additional and continued use of the term: Haematologica 1998: 83: 189-192 (see opening sentence); Blood 1999: 94:8: 2595-2604 (see Materials and Methods, first paragraph). Copies of these patents and literature articles were enclosed with the prior response of June 4, 2002, and the Examiner is requested to refer to that prior submission to review these materials. It is therefore submitted that claim 41 is definite.

As to claim 82, the passage objected to has been deleted, without admission, to expedite the current prosecution.

In view of the foregoing amendments and remarks, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, are solicited.

Claims 26, 29 and 87 were rejected in the Action under 35 U.S.C. § 102 (b) over Haberman. These claims have all been cancelled, thus rendering the rejections moot.

Claims 26, 29 and 87 were also rejected under 35 U.S.C. § 102 (a) over Ponting. The cancellation of these claims has also rendered this rejection moot.

Claims 26-31 and 87-90 were rejected under 35 U.S.C. § 103 (a) over Ponting or Haberman each taken with an asserted admission in the specification. These claims have been cancelled thus rendering this rejection moot.

Claims 11-14, 16, 23-39, 44, 45, 47-50, 52-53, 56-58, 62, 63, 67-69 and 79-93 were rejected under 35 U.S.C. § 103 (a) over Lim et al. taken with Williams and Patel (U.S. Patent No. 5,686,278) and further in view of an asserted admission as to prior art in the specification. In response, the inventorship of the claims presently pending in the application has been reviewed. It has been determined that inventor Patel should be added to the present application, which will make the inventorship of the '278 patent and the present application the same. Accordingly, the Williams and Patel '278 reference will be removed, thus overcoming the present rejection. The petition to correct inventorship is in process and will be submitted soon to the Examiner by facsimile. Withdrawal of this rejection is accordingly solicited.

Similarly, claims 11-23, 26-43, 52-61, 68, 69, 79-83, 87-89 and 91-93 were rejected under the Action under 35 U.S.C. § 102 (e) as being anticipated by, or in the alternative, under 35 U.S.C. § 103 (a), as being unpatentable over Williams and Patel '278. It is believed that the above-noted inventorship correction will also remove this rejection. Its withdrawal is therefore solicited.

Claims 11-23, 26-43, 52-61, 68, 69, 79-83, 87-89, and 91-93 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 5,686,278 or claims 1-14 of U.S. Patent No. 6,033,907. All of these claims, except claims 11-23, 38-43, and 79-83 have been cancelled. The rejection has thus been rendered moot relative to the

cancelled claims. As to the remaining claims, the requirement and availability of terminal disclaimers to overcome these rejections are being considered. A further response to this issue will be submitted along with the petition to correct inventorship.

In view of the foregoing amendments and remarks, and the submissions to be made, reconsideration and withdrawal of all rejections and allowance of this application containing claims 11-23, 38-43, and 79-83, are solicited. The Examiner is invited to telephone the undersigned attorney if there are any questions about this submission or other formal matters that may be handled in that fashion to expedite the allowance of this application.

Respectfully submitted

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VERSION WITH MARKING TO SHOW CHANGES MADE

38. (Amended) A cellular [population] composition comprising viable hematopoietic cells transduced by retroviral-mediated gene transfer in the absence of retroviral producer cells and in the presence of an immobilized amount of a polypeptide containing a first amino acid sequence which provides the binding activity of the Heparin-II binding domain of fibronectin and a second amino acid sequence which provides the cell-binding activity of the CS-1 domain of fibronectin, said immobilized amount of polypeptide being effective to increase the frequency of transduction of the hematopoietic cells by the retrovirus vector[.]; said composition also comprising said polypeptide.

82. (Twice Amended) The method of claim 81, wherein said domain has an amino acid sequence represented by the formula (SEQ.ID.NO. 1):

Ala Ile Pro Ala Pro Thr Asp Leu Lys Phe Thr Gln Val Thr Pro Thr Ser Leu Ser Ala Gln Trp Thr Pro Pro Asn Val Gln Leu Thr Gly Tyr Arg Val Arg Val Thr Pro Lys Glu Lys Thr Gly Pro Met Lys Glu Ile Asn Leu Ala Pro Asp Ser Ser Ser Val Val Val Ser Gly Leu Met Val Ala Thr Lys Tyr Glu Val Ser Val Tyr Ala Leu Lys Asp Thr Leu Thr Ser Arg Pro Ala Gln Gly Val Val Thr Thr Leu Glu Asn Val Ser Pro Pro Arg Arg Ala Arg Val Thr Asp Ala Thr Glu Thr Thr Ile Thr Ile Ser Trp Arg Thr Lys Thr Glu Thr Ile Thr Gly Phe Gln Val Asp Ala Val Pro Ala Asn Gly Gln Thr Pro Ile Gln Arg Thr Ile Lys Pro Asp Val Arg Ser Tyr Thr Ile Thr Gly Leu Gln Pro Gly Thr Asp Tyr Lys Ile Tyr Leu Tyr Thr Leu Asn Asp Asn Ala Arg Ser Ser Pro Val Val Ile Asp Ala Ser Thr Ala Ile Asp Ala Pro Ser Asn Leu Arg Phe Leu Ala Thr Thr Pro Asn Ser Leu Leu Val Ser Trp Gln Pro Pro Arg Ala Arg Ile Thr Gly Tyr Ile Ile Lys Tyr Glu Lys Pro Gly Ser Pro Pro Arg Glu Val Val Pro Arg Pro Arg Pro Gly Val Thr Glu Ala Thr Ile Thr Gly Leu Glu Pro Gly Thr Glu Tyr Thr Ile Tyr Val Ile Ala Leu Lys Asn Asn Gln Lys Ser Glu Pro Leu Ile Gly Arg Lys Lys Thr.

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Attorney Docket No. 7037-377

[or a sufficiently similar amino acid sequence thereto to exhibit retrovirus-binding activity of the Heparin-II domain of fibronectin.]